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| 09/788,308 | 02/16/2001 | Annelise E. Barron | 6374 | 7049 |

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| EXAMINER | |
|---|---|
| SCHNIZER, HOLLY G | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | |

DATE MAILED: 12/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/788,308 | BARRON ET AL. | |
| | Examiner | Art Unit | |
| | Holly Schnizer | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *18-27* is/are withdrawn from consideration.

5)☒ Claim(s) *30 and 31* is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) *28-29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7-22-02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Restriction/Election*

Applicants' election of Group I, claims 1-17 and 28-31, with traverse in the Response to the Restriction Requirement filed September 18, 2003 is acknowledged.

*Traversal:*

The traversal is on the grounds that the inventions are not independent and distinct because (1) the enhanced solubility and conformation control (Group II) can be achieved concomitantly to effect alveolar surfactant activity (Group III) and, (2) because neither method (Group II or III) can be practiced with another materially different composition. In addition, (3) Applicant argues that a search for the composition would encompass a search for the method and that there is no evidence of a serious burden of search.

*Restriction Requirement made Final:*

These arguments have been considered but are not deemed persuasive for the following reasons:

(1) As indicated in the previous Office Action, Groups II and III are independent and distinct because they have different modes of operation (different starting points, method steps, and endpoints), different functions and different effects (see MPEP 806.04 and 808.01). For example the method of Group III contains a step of administering the composition suggesting in vivo methods of treatment while Group II involves the an in vitro method of using the composition. While the methods of Group II and Group III may be overlapping they are not coextensive . Thus, for example, a

search for Group II would require considerations of administering the compound to a patient; a consideration not required for the methods of Group II.

(2) As indicated in the previous Office Action, inventions can be shown to be distinct if the product as claimed can be used in a materially different process of using that product (MPEP 806.05(h)). In the instant case, the product of Group I can be used in either of the processes of Group II or III, each of which is a materially different process from the other.

(3) As stated in the previous Office Action, a serious burden of search of each of the groups has been shown by their different classification and recognized divergent subject matter as defined by MPEP 808.02.

Thus, the restriction requirement is still deemed proper and is therefore made FINAL.

*Process claims may be rejoined if product claim is found allowable:*

The examiner notes that the present restriction is between product and process claims and applicant has elected claims directed to the product. Therefore, if a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever

is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

***Status of the Claims***

Claims 1-31 are pending. Claims 18-27 are withdrawn as being drawn to non-elected subject matter. Claims 1-17 and 28-31 have been considered on the merits in this Office Action.

***Failure to Comply with the Sequence Rules***

Where the description of a patent application discusses a sequence of 4 or more amino acids, reference must be made to the sequence by use of the sequence identifier preceded by "SEQ ID NO:" in the text of the description even if the sequence is also embedded in the text of the description of the patent application (see 37 C.F.R. 1.821, especially paragraphs (a)-(d)). The sequence identifier may be used in either the drawing or the Brief Description of Drawings (see MPEP 2429, helpful hint no. 21).

*Objection to the claims:*

Claims 28-29 are objected to for failure to comply with the sequence rules. Claim 28 recites an amino acid sequence containing the sequence PVHLKR. This section of the sequence requires a sequence identifier. Examples for overcoming this objection include adding PVHLKR to the sequence listing and amending the claim to refer to the sequence as: HN-$X_1X_2$(SEQ ID NO:##)$(NX_3)_n$-$CONH_2$ or adding Xaa Xaa PVHLKR to the sequence listing and amending the claim to refer to the sequence as: HN-(SEQ ID NO:##)$(NX_3)_n$-$CONH_2$. Claim 29 is objected to because it depends from Claim 28 yet does not correct its deficiency.

*Objection to the Specification:*

The Specification is objected to for failure to comply with the sequence rules for the same reasons as given above. The Specification refers to sequences without identifiers at page 12 (line 4), page 26 (line before Example 9), and Figure 7a (SPCM1-3) and 7b (SPCM 4-6). Correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-8 and 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 6, 7, 14, 16, and 17 are unclear as to whether the claimed spreading agent has been narrowed to encompass all of the claimed residues of the surfactant proteins B (for claims 3 and 14) or surfactant protein C (for claim 6, 7, 16, and 17); or whether the claimed protein encompasses any protein having at least one residue corresponding to residues 1-25 (claim 3 and 14) of SP-B or residues 1-35 (claim 6 and 16) or 5-32 (claim 7 and 17) corresponding to SP-C as recited in the independent claim 1 or 9. If the former was intended, then amending the claim to state, for example, "wherein said spreading agent comprises at least one N-substituted glycine residue and residues 1-25 of surfactant protein B" would be appropriate. If the latter was intended, then amending the claim to state, for example,, "wherein said spreading agent

comprises at least one N-substituted glycine residue and at least one amino acid residue corresponding to residues 1-25 of surfactant-associated protein B" would be more clear. Claims 4-5, 8, and 15 are rejected because they depend from the claims above but do not correct the deficiencies. Clarification is required.

Claims 3 and 15 are unclear as to what residues are being referred to in the recitation "said residues". Claims 1 and 9 (from which claims 3 and 15 depend, respectively) refer to "at least one N-substituted glycine residue" and "at least one amino acid residue corresponding to a natural surfactant-associated protein". Clarification is required. Claims 4 and 5 are rejected since they depend from rejected claim 3 yet do not correct its deficiencies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-natural heteropolymeric pulmonary spreading agent comprising a modified surfactant associated protein-C (SP-C) comprising at least one N-substituted glycine residue and wherein the modified SP-C maintains a membrane-spanning alpha helix and the activity of reducing alveolar surface tension or the non-natural heteropolymeric pulmonary spreading agents disclosed in the present Specification, does not reasonably provide enablement for a non-natural heteropolymeric pulmonary spreading agent comprising at least one N-

substituted glycine residue and any amino acid sequence or a modified surfactant protein B (SP-B) containing at least one N-substituted glycine residue . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the instant case, undue experimentation would be required to make the full scope of spreading agents that could be successfully used for their desired purpose (a spreading agent). Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

*Breadth of the Claims:*

The claims only require that the spreading agent contain at least one N-substituted glycine and at least one residue corresponding to either SP-B or SP-C. The phrase "at least one residue corresponding to" is interpreted as encompassing any protein with an amino acid in common with an amino acid found in SP-B or SP-C and thus encompasses any amino acid sequence that has at least one N-substituted glycine.

*Nature of the Invention:*

The invention involves the design polypeptoid spreading agents based on SP-B and SP-C sequences that will offer protease resistance and thus will have lower immunogenicity as compared to the natural surfactant associated proteins. With respect to spreading agents based on the SP-C sequence, evidence suggests that the SP-C sequence is less important than the maintenance of a membrane-spanning alpha helix for promoting rapid spreading of lipid mixtures (see Nilsson et al. discussed below). On the other hand, evidence suggests that a simple amphipathic helical peptide does not mimic the surface properties of SP-B (see Nilsson et al. discussed below). Furthermore, SP-B is significantly larger than SP-C and has a tertiary fold of several amphipathic helices in a dimeric structure. Thus, it appears that a membrane spanning alpha helix is required to maintain the activity of SP-C and that making a synthetic spreading agent with N-substituted glycines based on SP-B sequence is highly complex.

*Amount of direction or guidance presented and Presence or Absence of Working Examples:*

The present Specification refers to several references to show that making polypeptoids is well known in the prior art. The Specification provides several examples of the production of a variety of polypeptoid spreading agents based on the sequence of SP-C. The examples show that the SP-C based polypeptoids improve surface activity, improve respreading of DPPC, and that addition of SP-C mimics to lung surfactant does

not adversely effect static and dynamic behavior of the lung surfactant. Example 8 provides evidence that the SP-C mimics maintain a helical secondary structure like that of natural SP-C.

There are no examples of SP-B based polypeptoids and the Specification does not provide any guidance as to how such molecules could be made that would maintain the activity of reducing alveolar surface tension possessed by the natural SP-B.

*State of the prior art and Relative skill of those in the prior art:*

The prior art provides evidence that the SP-C primary structure (sequence) is not as important as its secondary structure (maintaining its transmembrane alpha helical structure) and that one of ordinary skill in the art was able to make mutations in the protein and maintain the alpha helical structure (see Nilsson et al. Eur. J. Biochem. (1998) 255: 116-124; specifically p. 123, Col. 2, 1st paragraph). Nilsson et al. show that an optimally alpha helical SP-C based substitute (WMAP10; see p. 121, Col. 1, 2nd paragraph and Fig. 1) and an SP-C based substitute wherein all helical valine residues are replaced with Leucines and the palmitoylcysteines at positions 5 and 6 are replaced with serine maintains its helical structure and spreading properties of native SP-C. Thus Nilsson et al. appears to provide evidence that the SP-C sequence may be modified considerably without loss of activity as long as its transmembrane alpha helical nature is not disturbed and that those of skill in the art were able to optimize the helical nature of SP-C.

Nilsson et al. also describe the properties of a peptide with an amphipathic helix that resembles the helices of SP-B but that does not accelerate lipid spreading

effectively (p. 120, section spanning columns) like SP-B. Nilsson et al. conclude that SP-B is a much more complex molecule than SP-C.

*Predictability:*

For the reasons stated above, designing a peptoid having any sequence or a peptoid based on the SP-B sequence that would maintain the property of reducing alveolar surface tension possessed by natural SP-B and SP-C is highly unpredictable.

*Quantity of Experimentation*:

Because the claims only require one amino acid in common with SP-B and SP-C, a large quantity of experimentation would be necessary to generate the infinite number of polypeptoid molecules recited in the claims and possibly screen same for activity.

To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the characterization of the properties of SP-B which are required to maintain its activity and the discovery of active SP-C mimics that do not have alpha helical structure. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a spreading agent which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

***Conclusions***

Claims 1-17 are rejected. Claims 28-29 are objected to. Claims 30-31 appear to be in condition for allowance.

A thorough search of the prior art including a sequence search of SEQ ID NOs: 1-4 did not reveal any teachings or suggestions of the peptoid based SP-C mimics disclosed in the Specification or of modifying surfactant associated proteins to include N-substituted glycine residues as has been done in the present invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm. ***The examiner has been tentatively scheduled to move to the new office on January 8, 2003. After this date, the examiner may be reached at (571) 272-0958.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
December 5, 2003

CHRISTOPHER S. F. LOW
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